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Monosomy 6q1: Syndrome Delineation

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We report on a girl with a de novo 6q1 interstitial deletion. To our knowledge, this is the second reported case with a deletion of 6q11–q15. We review the phenotype of monosomy 6q1. Our patient has manifestations similar to others with monosomy 6q1 including mental deficiency, growth retardation, short neck, and minor facial anomalies.

KEY WORDS: chromosome 6, interstitial deletion, multiple congenital anomalies, mental retardation, gingival hypertrophy, dental fusion

INTRODUCTION

To date, ten individuals have been reported with various interstitial deletions in band 1 of the long arm of chromosome 6. In addition, six cases are documented in which the interstitial deletion spans parts of bands 1 and 2. The clinical spectrum of 6q1 monosomy has been reported to include short neck, round face with or without asymmetry, various minor facial anomalies, congenital heart defect, umbilical hernia, an excess of whorls on finger pads, transverse palmar creases, postnatal growth deficiency, mental retardation, and hypotonia. We report on a girl with the second known case of the interstitial deletion 6q11–q15 with comparison to other 6q1 monosomy patients.

CLINICAL REPORT

A Caucasian girl was born by spontaneous breech delivery at 39 weeks of gestation to a 35-year-old G3P1011 mother and 44-year-old father. During the pregnancy, the mother experienced pelvic discomfort and low back pain. Maternal weight gain was 22.7 kg. Previous pregnancies included a healthy boy and a blighted ovum. Following the patient's birth, the fourth pregnancy also resulted in a blighted ovum and the fifth pregnancy produced a healthy daughter. Family history was otherwise unremarkable and nonconsanguineous.

Birth weight was 3,370 g (50th centile), length was 50.8 cm (70th centile), and head circumference (OFC) was 33.0 cm (40th centile). Genetic consultation at day 1 of age showed prominence of the lower occiput, a short neck with webbing, low posterior hairline with midline descent, apparently low-set ears with the upper helix folded on the right ear, retrognathia, and anteriorly displaced anus, and generalized hypotonia. Capillary hemangiomata were present on both upper eyelids, tip of the nose, glabella, and the base of the nares. Figure 1 shows the patient at age 2 weeks.

At age 6 months, she had bilateral epicanthal folds, ear length of 5.2 cm (97th centile), facial asymmetry with prominent right side, smooth philtrum, high-arched palate, umbilical hernia, midline sacral pit, and mild lower back hypertrichosis. "Flaps" of excess gingiva were attached to the posterior maxillary and mandibular alveolar ridges. Dermatoglyphics showed four whorls and six ulnar loops on fingertips, transverse palmar crease on the right, and a bridged palmar crease on the left. Mild general hypotonia was present. Grade IV left vesicoureteral reflux was reported.

At age 1 year, the right side of the face remained prominent. Palpebral fissures were short and slightly upslanting. The "flaps" of gingival tissue connected to the mandibular and maxillary alveolar ridges had increased in size from the previous evaluation. The primary mandibular right lateral incisor and canine were fused (Fig. 2). Mild retrognathia was evident.

At age 3.3 years (Fig. 3), the following features were evident: short neck with webbing, large ears, smooth philtrum, mild retrognathia, and abundant, light colored scalp hair. Reimplantation of the ureters resulted in normal kidney function with occasional recurrent urinary tract infections.

Psychomotor development was delayed. The patient sat at 17 months and stood at 22 months. Since age 2 years, walking has been assisted by lower leg braces and a walker. Her first words were reported to be "hi" and "mama" at age 6 months; however, she did not form

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Fig. 1. Patient at age 2 weeks.

Fig. 2. Gingival hypertrophy and fusion of primary mandibular right lateral incisor and canine teeth.

sentences until after speech therapy was instituted at $2^{8}/_{12}$ years. The patient had some degree of tactile defensiveness and was sensitive to loud noises.

At age 5 years, the patient was making encouraging progress with motor and verbal skills. Latent nystagmus with intermittent left esotropia was present. The "flaps" of gingival tissue were no longer evident. The patient was using small ankle braces and no longer uses a walker. The family also reported their daughter has a "very warm, loving nature."

CYTOGENETIC STUDIES

Cytogenetic analysis was performed at the 550 GTG banding level on chromosomes prepared from peripheral lymphocyte cultures. A deletion of chromosome 6 was demonstrated, 46,XX,del(6)(q11q15), in 100 metaphase spreads analyzed (Fig. 4). Evaluation of 100 cells excludes mosaicism of this structural alteration (>2% at 95% confidence level). Identification of the 6q11–q15 deletion was consistent with a further 23 cells from skin fibroblast cultures analyzed at the 400 GTG banding level. Parental chromosomes were normal.

Dual color molecular cytogenetic FISH was performed using a COATASOME total chromosome 6 probe and a chromosome 6 alpha-satellite probe that hybridizes to the highly repetitive alphoid DNA located at the centromere (Oncor, Inc.). Lack of aberrant hybridization signal from the FISH studies on 30 cells confirmed the Giemsa banded observation that the 6q11–q15 deleted chromosomal segment was not involved in a translocation rearrangement with another chromosome.

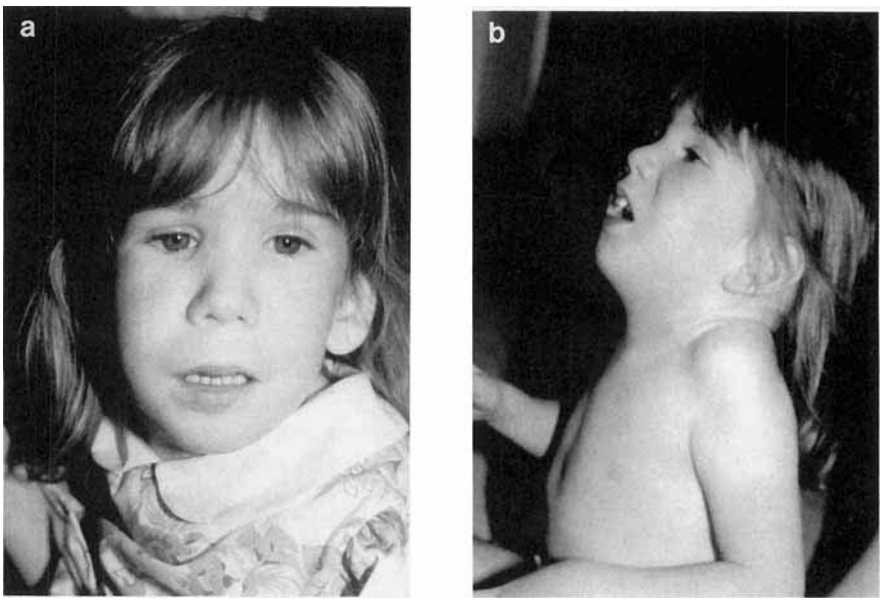

Fig. 3. **a,b:** Patient at age 3.3 years.

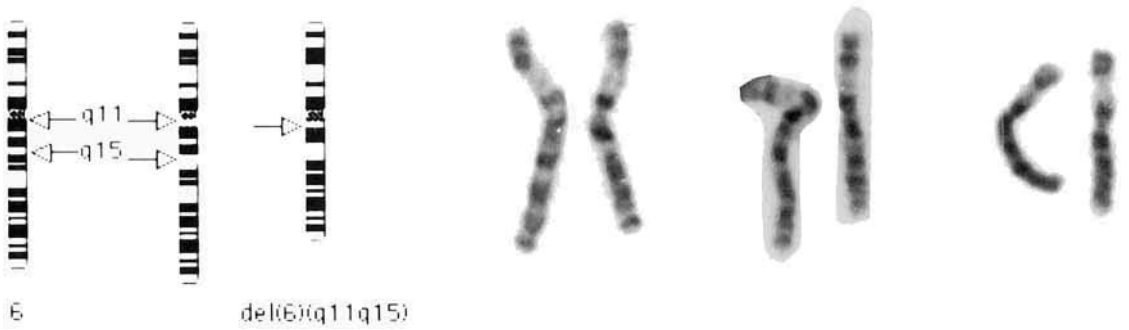

Fig. 4. GTG-banded chromosomes, at 550 band level, prepared from peripheral lymphocyte cultures demonstrating a deletion of 6q11–q15 on the right chromosome in each pair.

DISCUSSION

Reported 6q1 deletion patients are listed in Table I. Two patients with deletions of 6q16–q22 [Chery et al., 1989; Côté et al., 1981] were excluded based upon the authors' reports of band 6q16 appearing intact. A patient reported to have a 6q11–q14 deletion [Voullaire et al., 1989] was excluded following a personal communication from the author [Voullaire, personal communication] stating that the patient was subsequently reviewed and does not have a 6q deletion.

Of the 17 patients reported to have partial 6q1 monosomy, a deletion of 6q11–q15 has been reported in only one other child [Slater et al., 1987]. Findings common to both individuals include psychomotor delay, poor feeding, various minor facial anomalies, short neck, and umbilical hernia (Table II). Unlike Slater's patient, our patient was appropriate in size for gestational age and did not begin to show growth delay until age 1 year. Figure 5 shows the initially marked decreasing growth parameters of our patient as measured in centiles at birth and ages 6 months, 1 year, and 3.3 years. However, she has made notable progress as shown both by her centiles at age 5 years and her most recent clinical description.

Patients with 6q1 deletions appear to share many common anomalies. Table III summarizes the characteristics found in at least 50% of the known 6q1 deletion cases. The ratio of males to females reported with 6q1 deletions is approximately 1:1. Both sexes appeared to have similar phenotypic effects. In addition to

TABLE I. Reported 6q1 Deletion Cases

Deletion	Cases	Authors
6q11–q15	2	Our patient, Slater et al., 1987
6q12–q14	1	Lonardo et al., 1988
6q13–q15	4	Rose et al., 1992; Yamamoto et al., 1986; Young et al., 1985; McNeal et al., 1977
6q13–q21	1	Wakahama et al., 1991
6q14–q16	4	Roland et al., 1993; Valtat et al., 1992; Turleau et al., 1988
6q15–q21	3	Horigome et al., 1991; Glover et al., 1988; Nakagome et al., 1980
6q15–q22	1	Fryns et al., 1991
6q16–q22	1	Schwartz et al., 1984

TABLE II. Comparison of Interstitial Deletion 6q11–q15 Patients*

Characteristic	Slater [1987]	Our patient
Maternal age	16	35
Paternal age	?	44
Birth weight	3rd centile	50th centile
Head circumference	3rd centile	40th centile
Psychomotor delay	+	+
Hypotonia	NR	+
Poor feeding	+	+
Short neck	+	+
Webbed neck	NR	+
Low anterior hairline	NR	+
Round face	NR	+
Malformed ears	–	+
Epicanthus	NR	+
Retro/micrognathia	+	+
High-arched palate	+	+
Smooth/shallow philtrum	+	+
Thin upper lip	+	+
Anteriorly displaced anus	NR	+
Long fingers	+	–
Long flat feet	+	–
Prominent heels	+	–
Umbilical hernia	+	+

* +, characteristic present; –, characteristic not present; NR, not reported.

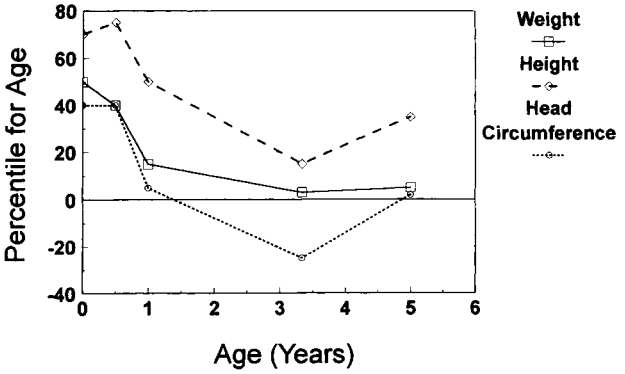

Fig. 5. Growth parameters remove in centiles with age.

TABLE III. Characteristics Reported in at Least 50% of the 17 Patients With 6q1 Monosomy

Characteristic	Percent reported
Sex	
Male	59
Female	41
Mental deficiency[a]	100
Growth retardation	82
Short neck	53
Round face	65
Malformed ears	71
Abnormal palpebral fissures	59
Epicanthus	59
Wide nasal bridge	65
Abnormal philtrum	71
Thin lips	59
Micrognathia	53
Congenital heart defect	53

[a] Mental ability was not evaluated in four patients: one patient was 3 months of age at report [Lonardo et al., 1988] and three patients were fetal or neonatal deaths [Fryns et al., 1991; Nakagome et al., 1980; Wakahama et al , 1991].

the more frequently reported findings, the following anomalies were observed in <50% but over 25% of patients: microcephaly, facial asymmetry, hypertelorism, high-arched palate, umbilical hernia, renal abnormalities, scoliosis/kyphosis, abnormal palmar creases, and hypotonia. A predominance of whorl patterns on the finger pads was reported in five of eight examined patients [Nakagome et al., 1980; Schwartz et al., 1984; Turleau et al., 1988; Yamamoto et al., 1986; Young et al., 1985]. Of interest, gingival hypertrophy was reported in a 6q12–q14 deletion patient [Lonardo et al., 1988] in addition to our patient. Various unique findings included blue sclerae [Lonardo et al., 1988], ocular albinism [Rose et al., 1992], cleft palate [Yamamoto et al., 1986], absent maxillary lateral incisors [Young et al., 1985], and T-E fistula [McNeal et al., 1977].

In conclusion, the emerging 6q1 monosomy syndrome appears to include varying mental deficiency, growth retardation, and minor facial anomalies often with a short neck. The relatively mild degree of clinical features in 6q1 monosomy patients is of particular interest when considering the large size of these deletions. More cases are certainly needed to accurately assess this phenotype and discern the genes affected by this deletion.

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